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AN EVALUATION OF BIS(DIALKYLAMINO) AND BIS(DIARYLAMINO)ALANES AS STEREOSELECTIVE AND FUNCTIONAL GROUP REDUCING AGENTS TOWARD ORGANIC SUBSTRATES

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AS STEREOSELECTIVE AND FUNCTIONAL GROUP REDUCING AGENTS

TOWARD ORGANIC SUBSTRATES

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Chairman

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SUMMARY

An extensive study of the reduction of five representative cyclic ketones was carried out. The reductions were carried out using bis(dialkylamino) and bis(diarylamino)alanes as the reducing agents. These hydrides had not previously been evaluated as reducing agents. The precursor to these hydrides [$AlH_3N(CH_3)_3$] was also evaluated as a reducing agent.

Each ketone was carefully selected so that the information gained from its reduction products could be meaningful. The ketones reduced were 2-methylcyclohexanone; 3,3,5-trimethylcyclohexanone, 4-t-butylcyclohexanone, camphor, and norcamphor. Each of these ketones presented different steric requirements and the reduction of each was hoped to give important information concerning the reducing capability of the hydrides.

The hydrides used in these reductions were bis(diethylamino)alane, bis(diisopropylamino)alane, bis(diphenylamino)alane, and the precursor to these, trimethylamine alane. Each of these hydrides have different steric requirements and provide important information concerning the reactivity of the hydrides as well as the stereochemistry of the reactions involved.

The effect of solvent in these reductions was also evaluated. The reductions were carried out in benzene, diethyl ether, and tetrahydrofuran. Each reduction reaction was carried out for two hours at 0°C when diethyl ether and tetrahydrofuran were the solvents. However, due to the freezing point of benzene, the reductions in this solvent were carried

out at room temperature for two hours.

The effect of concentration on stereochemistry was determined. These reactions were carried out only in benzene using 3,3,5-trimethylcyclohexanone and camphor as the organic substrates.

The effect of temperature on the stereochemistry was also evaluated. In these reactions 3,3,5-trimethylcyclohexanone and camphor were reduced by $[(i\text{-}Pr)_2N]_2AlH$ in diethyl ether solvent.

The general preparation of the hydrides used in these studies is given in the following equations. Equation (1) describes the preparation of the precursor, trimethylamine alane. Equation (2) describes the preparation of the bis(dialkylamino) and bis(diarylamino)alanes.

$$LiAlH_4 + Me_3NHCl \xrightarrow{\text{ØH}} H_3AlNMe_3 + LiCl\downarrow + H_2\uparrow \qquad (1)$$

$$AlH_3NMe_3 + 2(HNR_2) \xrightarrow{\text{ØH}} HAl(NR_2)_2 + Me_3N\uparrow + 2\ H_2\uparrow \qquad (2)$$

The yields in these reactions were quantitative and the $HAl(NR_2)_2$ compounds were found to be stable in benzene over several months at room temperature. Reaction in THF and Et_2O were carried out by adding a small aliquot of a concentrated solution of the hydride in benzene to the organic substrate in the ether solvent.

An additional evaluation of these hydrides was made by reducing selected functional groups. The same hydrides were allowed to react with compounds containing different functional groups for two hours and twenty-four hours. These reactions were run for two different periods of time in order to evaluate the possibility of reducing one functional

group in the presence of another. The functional group reductions were carried out in benzene solvent, and several interesting results were obtained.

CHAPTER I

INTRODUCTION

In recent years a great amount of chemical literature has been devoted to selective reductions using metal hydrides as reducing agents. The reducing action of lithium aluminum hydride was studied extensively using THF as the solvent. Excess lithium aluminum hydride was allowed to react with fifty-six selected organic compounds containing representative functional groups.[1] At the same time aluminum hydride was also evaluated as a reducing agent under the same conditions as those used in the evaluation of lithium aluminum hydride. A comparison was made between the two reducing agents.[2] It was found from this comparison that aluminum hydride exhibited some interesting differences as a reducing agent.[3] These differences cause one to reason that in $HAlX_2$ compounds where $X = NR_2$ still further interesting differences from those found between $LiAlH_4$ and AlH_3 should be observed.

The preparation[4-7] and reactions[2,8-14] of lithium alkoxy-aluminum hydrides have also been studied extensively in recent years. In particular, the stereoselectivity of lithium-tert-butoxyaluminum hydride has been examined, however, strange and unexplained results have been observed.[14]

Complex metal hydride selectivity in reductions has been thought to depend on the steric bulk of the reducing agent as well as the steric requirements of the organic substrate; a larger hydride molecule was ex-

pected to give a larger yield of the products formed from the attack of the hydride at the least hindered side of an asymmetric molecule. The data obtained through the experiments in this study show that there must be other factors besides these two steric interactions involved in the stereoselectivity of the reducing agents evaluated.

There are two ways in which the term "selective reductions" can be used. It can be used to refer to the reduction of one functional group in the presence of another and it can be used to describe the reduction to one of several possible products. The term will be used in both ways throughout this study, but there should be no confusion, because the stereoselective evaluation will be discussed separately.

Aminoalanes have been used as polymerization catalysts,[15] reducing agents,[16] and as synthetic intermediates.[17] These compounds can be prepared by reaction of alane or trimethylamine alane[19] with secondary amines (equation 1) or by reaction of lithium aluminum hydride with dialkylammonium chloride (equation 2).[20]

$$AlH_3 + nHNR_2 \rightarrow nH_2 + H_{3-n}Al(NR_2)_n \qquad (1)$$

$$n = 1, 2, \text{ and } 3$$

$$LiAlH_4 + R_2NH_2Cl \rightarrow LiCl\downarrow + 2\ H_2\uparrow + H_2AlNR_2 \qquad (2)$$

Another preparation for these compounds is through direct synthesis from aluminum, hydrogen and secondary amines (equation 3).[21]

$$Al + H_2 \xrightarrow{R_2NH} HAl(NR_2)_2 \qquad (3)$$

The method used for the preparation of the bis(dialkylamino) and bis(diarylamino)alanes during these experiments was the one described by equation (1). Trimethylamine alane was the starting material used to react with the secondary amines. There were several reasons for selecting equation (1) as the method of choice, but primarily this method was the simplest and the reactions could be carried out in benzene. This preparation allowed the hydrides to be stored in hydrocarbon solvent with no chance of ether cleavage by the hydrides.

Prior to these evaluations no detailed study had been made concerning the reductions involving bis(dialkylamino) and bis(diarylamino)alanes. This study is a natural continuation of the interest in this laboratory evaluating $HAlX_2$ compounds where X = hydrogen, halogen, alkoxy, dialkyl(aryl)amino, and hydrocarbon as selective reducing agents in organic chemistry.

Since it would be important to compare the reduction data of the bis(dialkylamino)alanes with that of known compounds, data for $LiAlH_4$ and AlH_3 reductions of each substrate also appears in the tables.

CHAPTER II

EXPERIMENTAL

Instrumentation and Apparatus

The inert atmosphere glove box used in these studies was manufactured by Kewaunee Manufacturing Company (Model 2C1020) and was equipped with a recirculating system in order to continuously remove oxygen and water from the system. A Little Giant pump (capacity 1.25 cfm) was used to recirculate the atmosphere.

All chromatographic analysis were carried out using a dual column gas chromatograph (F+M Scientific Model 720) using columns containing Carbowax 20 M or diglyceral suspended on chromosorb G-NAW (60/80 mesh).

The nmr spectra were obtained using a Varian A-60 spectrometer.

The mass spectra were obtained using a Varian M-66 spectrometer.

Reagents

Lithium and sodium aluminum hydride (Ventron Metal Hydrides Division) were used as drying agents without further purification. Lithium aluminum hydride (Ventron Metal Hydrides Division) was used in the preparation of trimethylamine alane without further purification.

Tetrahydrofuran (Fisher Certified), benzene (Baker Thiophene-free), were distilled from $NaAlH_4$ through a two foot vigreaux column under dry nitrogen just prior to use. Diethyl ether (Fisher Certified)

was distilled from $LiAlH_4$.

The liquid ketones, 2-methylcyclohexanone and 3,3,5-trimethylcyclohexanone (both Eastman Certified) were dried over anhydrous $MgSO_4$ prior to vacuum distillation. The solid ketones, 4-t-butylcyclohexanone, camphor, and norcamphor (all Eastman Certified) were purified by sublimation under vacuum.

The liquid secondary amines (diethylamine, diisopropylamine, and 2,6-dimethylpiperidine) were purified by drying over anhydrous $MgSO_4$ followed by distillation under a dry nitrogen atmosphere. The solid diphenylamine was purified by sublimation under vacuum.

The liquid compounds used in the functional group reduction study (styrene, styrene oxide, benzoylchloride, ethyl benzoate; 1-phenyl, 2-chloroethane; and benzladehyde) were purified by drying over $MgSO_4$ followed by vacuum distillation. All of these compounds were Eastman Certified) and N,N-dimethylbenzamide (Eastman Certified) were purified by sublimation under vacuum.

The trimethylaminehydrochloride (Eastman Certified) was used without further purification.

All manipulations of air sensitive compounds were carried out in the glove box or on the bench top using Schlenk tube techniques.[21] All equipment that came in contact with the reagents was dried by flash flaming under vacuum or under rapid nitrogen purge prior to use.

Preparations

Preparation of Trimethylamine Alane

The preparation of trimethylamine alane was carried out in benzene

solution. A maximum of one fourth mole of the compound was prepared at a time.

A 500 ml 24/40 standard tapered ground glass three-neck boiling flask which had been flamed and equipped with a one-inch magnetic stirring bar was taken into the glove box. At the same time 250-300 milliliters of dry benzene were also taken into the glove box in a separate flask. $LiAlH_4$ was stored in the glove box and an excess (15 grams) was weighed on a triple beam balance inside the glove box. The $LiAlH_4$ powder was then added to the three-neck flask equipped with the stirring bar. The benzene was then poured into the three-neck flask over the $LiAlH_4$ powder. A slurry was made since the $LiAlH_4$ was insoluble in the benzene. The three-neck boiling flask was then sealed with ground glass 24/24 standard tapered stoppers. Rubber bands were wrapped around these stoppers to hold them tightly closed. The flask was then removed from the glove box.

One fourth mole (24 grams) of trimethylamine hydrochloride was also weighed out in the glove box on the triple beam balance. This compound was put into a dry six inch Schlenk tube while still in the glove box. The Schlenk tube was sealed by a 24/40 standard tapered ground glass stopper and was brought out of the glove box.

The following operations should be carried out in a hood. A Friedricks' condenser equipped with a 24/40 standard tapered joint and with dry nitrogen flow was placed on the three-necked flask with the benzene, $LiAlH_4$ slurry in it. One side (24/40 standard tapered outer) joint on the three-neck flask was equipped with a 24/40 standard tapered stopper equipped with a 3-way stopcock. Aliquots of the solution

could be removed for analysis through this stopcock without air or moisture getting to the solution. The remaining side 24/40 standard tapered joint was attached to the Schlenk tube by way of a 3/4 inch diameter curved (45° angle) adapter equipped with 24/40 standard tapered ground glass inner joints at each end. This set up allowed transfer of the solid Me_3NHCl into the slurry. All the preceding manipulations were carried out under constant dry nitrogen flow through both the Schlenk tube containing Me_3NHCl and the condenser on the three-neck flask containing the $LiAlH_4$ in benzene.

When the Schlenk tube was attached and the apparatus was completely sealed from the outside atmosphere the solid Me_3NHCl was added very slowly to the slurry by twisting and turning the Schlenk tube to allow the solid Me_3NHCl to fall into the slurry.

The nitrogen gas flow was regulated through an oil bubbler so that gases given off during reaction could escape. The reaction was initially very mild but as it proceeded much H_2 was evolved and the solid Me_3NHCl was added carefully and slowly until H_2 evolution ended.

The following equation represents the reaction as described.

$$LiAlH_4(\text{Excess}) + Me_3NHCl(\text{solid}) \xrightarrow{\emptyset H} LiCl + H_2 + H_3AlNMe_3$$

The solution of H_3AlNMe_3 was then taken into the glove box and the excess $LiAlH_4$ and the LiCl were removed by filtering the solution through a 300 ml sintered glass filter. The solution after filtration was clear and colorless. The solution was sealed with a 24/40 standard tapered ground glass stopper and removed from the glove box. A 2 milli-

liter sample of the solution was analyzed for both H_2 and aluminum.

Analyses were performed by hydrolyzing a sample with a water-acid mixture followed by determination of the hydrogen content by gas evolution analysis. Aluminum, in the same sample, was determined by EDTA titration.

The preceding preparation of the Me_3NAlH_3 was carried out on 3 different occasions during this study and the following analyses were found at time of preparation. The first sample which was prepared on July 28, 1970 had a H_2 to Al ratio of 2.87 to 1 and was .76 molar in Me_3NAlH_3. The second sample prepared on October 8, 1970 had a H_2 to Al ratio of 3.08 to 1 and was .52 molar in Me_3NAlH_3. The third sample had a H_2 to Al ratio of 2.82 to 1 and was .86 molar in Me_3NAlH_3.

In each preparation the yield was quantitative, the Al:H_2 ratio was nearly 1:3 and the hydride was stable in benzene for several months. This stability was checked frequently by doing further analysis on the solution. Each analysis was found to be within experimental error of the previous one.

The Preparation of Bis(diethylamino)alane and Bis(diisopropylamino)alane

Bis(diethylamino)alane and bis(diisorpropylamino)alane were also prepared on three different occasions. In each preparation 75 millimoles of each compound was prepared. The compounds were prepared by adding 2 millimoles of the secondary amine for each millimole of trimethylamine alane. Therefore, in each preparation 150 millimoles of the secondary amine were added to 75 millimoles of trimethylamine alane.

All operations were carried out under dry nitrogen atmosphere and the same precautions were taken in these preparations as in the prepara-

tion of trimethylamine alane. The amines were added through a separatory funnel equipped with a 24/40 standard tapered ground glass inner joint. The 150 millimoles of amine were added to 75 millimoles of trimethylamine alane through one of the side necks of a 3-neck 100 ml boiling flask with 24/40 standard tapered ground glass outer joints. The boiling flask was also equipped with a 3/4 inch magnetic stirring bar. The amine was added drop by drop from an addition funnel and H_2 was rapidly evolved which escaped through the oil bubbler. The following equation represents the preparation of this class of compounds.

$$Me_3NAlH_3 + 2\ HNR_2 \longrightarrow (R_2N)_2AlH + H_2 + NMe_3$$

The reaction in the preparation of bis(diethylamino)alane was very fast and proceeded without any difficulty to completion in quantitative yield. However, the preparation of bis(diisopropylamino) alane required that the reactants in solution be refluxed for 48 hours before complete reaction was effected.

After the reactions were completed, the solvent and any excess amine were stripped from the compound under vacuum and the white solid hydrides were again dissolved in benzene.

The solutions were analyzed in the following way. Sample one of bis(diethylamino)alane had a H_2 to Al ratio of 1.0075 to 1. Sample two had a H_2 to Al ratio of 1.06 to 1 and sample three had a H_2 to Al ratio of 1.1 to 1. Sample one of bis(diisopropylamino)alane had a H_2 to Al ratio of 1 to 1.102. Sample two had a H_2 to Al ratio of 1.09 to 1 and sample three had a H_2 to Al ratio of 1.1 to 1. All solutions analyzed

within experimental error of the 1 to 1 ratio expected.

The Preparation of Bis(diphenylamino)alane

Preparation of bis(diphenylamino)alane was carried out in the same way as the preparations of bis(diethylamino)- and bis(diisopropylamino)alane. However, since diphenylamine was a solid it had to be dissolved in benzene and added to the trimethylamine alane solution by addition through the side neck of the three-neck flask. The bis(diphenylamino)alane was found to be insoluble in benzene and diethyl ether. Therefore, a filtration was performed inside the glove box in order to remove the solid hydride. The solid was dried under vacuum at 80°C and was stored under vacuum in the inert atmosphere box as a solid.

A weight analysis was performed on a .1113 gram sample of the compound and the results were the following. The calculated weight percent of H_2 was .273%. The actual weight percent found for H_2 was .222%. The calculated weight percent for Al was 7.377%. The actual weight percent found in the sample for Al was 7.053%. These actual weight percentages were very close to the calculated ones and confirmed the formation of bis(diphenylamino)alane.

The Preparation of Bis(2,6-dimethylpiperidino)alane

Bis(2,6-dimethylpiperidino)alane was prepared somewhat differently from the other aminoalanes because in this preparation the solvent was the secondary amine itself. The solution of 2,6-dimethylpiperidine and 50 millimoles of trimethylamine alane (benzene solution) were refluxed for 4 days. The result was the formation of the compound bis(2,6-dimethylpiperdino)alane. The analysis showed a H_2 to Al ratio of .99 to 1.

The excess amine and benzene were stripped from the hydride by vacuum and the compound was redissolved in benzene.

Preparation of the Ketone Solutions

Each ketone to be reduced was weighed (~ 20 millimoles) into a dry 100 ml volumetric flask. The dry solvents: benzene, THF, and diethyl ether were added to make a total volume of 100 milliliters, or a solution that was 0.2 molar in the respective ketone. A total of fifteen different ketone solutions were prepared. Five different ketones were dissolved in three different solvents. This process allowed the solutions of the respective ketones to be made in the three solvents immediately prior to reduction. The volumetric flasks were equipped with ground glass stoppers to avoid evaporation of the solvent.

Ketone solutions were always freshly prepared, because solutions of these ketones were found not to be stable in ether solvents. For this reason the reduction of a particular ketone was carried out with all the hydrides at the same time just after preparing the ketone solution.

General Method of Stereoselective Reductions

The stereoselective reductions were carried out in 50 milliliter Erlenmeyer flasks equipped with rubber septum caps and 3/8 inch magnetic stirring bars. These flasks were placed on a manifold with 12 nitrogen outlets which had a piece of tygon tubing approximately 2 inches long with a No. 22 gauge syringe needle attached to each nitrogen outlet. The manifold was attached at one end to an oil bubbler and at the other end to a source of dry nitrogen. This apparatus allowed the 50 milliliter reaction flask to be kept under a constant internal pressure of dry

nitrogen. Before any reagents were added to these 50 millilter flasks, the septum caps were placed on them and the flasks were attached to the manifold by piercing the septum caps through the top with the syringe needle. After the flasks were attached to the manifold, they were flame dried 2 or 3 times under a flow of dry nitrogen.

The hydride (3 milliequivalents) was added to the flask. Twelve reductions were carried out at the same time. Each of the four reducing agents was evaluated in three different solvents with one ketone. The four reducing agents first evaluated were: $(Et_2N)_2AlH$, $(i\text{-}Pr_2N)AlH$, $(Ph_2N)_2AlH$ and Me_3NAlH_3. The hydride solutions were approximately 3 molar. Therefore, the reductions only required 1 milliliter of the hydride solution for each reduction when bis(diethyl)- and bis(diisopropylamino)alane were the reducing agents. Approximately 0.4 milliliteres of the trimethylamine alane solution was required for each reduction. The bis(diphenylamino)alane was allowed to react as a solid and was weighed into the 50 milliliter Erlenmeyer flasks while inside the glove box. In each reduction 3 milliequivalents of the hydride was added.

The flasks in which the reductions were to be carried out in diethyl ether and THF were cooled by an ice bath to 0°C before addition of the ketone solutions. The flasks in which the reductions in benzene were to be carried out were not cooled. The hydrides in solution were added by syringe as were the ketone solutions. The needles of the syringes were simply used to pierce the septum cap and the addition was affected. The syringes had previously been flamed dried and flushed with dry nitrogen. Approximately 10 milliliters (2 millimoles of ketone) of the

ketone solutions were added to each of the twelve flasks and the reactions were allowed to stir for 2 hours. At the end of two hours the solutions were quenched with 1 milliliter of a saturated solution of ammonium chloride (Eastman Certified).

A standard solution (containing an internal standard, the ketone and expected products) was prepared for each ketone. The compounds were weighed into a 3 dram vial using a Mettler balance. This solution was then subjected to gas chromatography and the response ratios for the ketone and expected products were obtained.

The internal standards were checked for stability in the reaction mixtures by adding a weighed amount of the respective standard to a quenched reaction. This reaction was then analyzed by gas chromatography and allowed to sit covered by a septum cap for one week. After one week another analysis was made and there was no change in the results. Therefore, there was no further reaction of the standard with anything in the quenched reaction mixture, and there was no equilibration of the respective alcohols.

Results

The reduction of 2-methylcyclohexanone were carried out in the manner previously described. The internal standard (3,3,5-trimethylcyclohexanone) was weighed into the quenched reaction mixtures. A 12 foot 10% diglycerol column was used to make the separation on the gas chromatograph. The results of these reductions are shown in Table 1.

The conditions for the gas chromatographic separations were the following. The flow rate of He was 60 cc per minute. The oven tempera-

was 75°C. The detector temperature was 290°C and the temperature of the injection port was 260°C. A 24 μl sample was injected and the attenuation was set on 2. The retention times for the 2-methylcyclohexanone under these conditions was 8 minutes. Retention times for the axial and equatorial alcohols were 18 and 24 minutes respectively. The retention time for 3,3,5-trimethylcyclohexanone was 11 minutes. The response ratios were essentially one to one on a molar scale. The compounds in the organic layer of the solution were separated completely by gas chromatograph and the peaks were easily measured by planimetry.

The results in Table 1 show that the bis(dialkylamino)-and bis-(diarylamino)alanes gave more equatorial attack yielding a larger percentage of the axial alcohol. Trimethylaminealane, AlH_3 and $LiAlH_4$, however, gave more equatorial alcohol formation. Neither of the bis(dialkylamino)- or bis(diarylamino)alanes was as reactive as trimethylamine alane.

The trimethylamine alane showed very similar results to those found when AlH_3 was used to reduce 2-methylcyclohexanone. This similarity would suggest that either Me_3NAlH_3 dissociates in solution to AlH_3 or that the steric requirement of Me_3NAlH_3 and $THFAlH_3$ is about the same.

The reductions of 3,3,5-trimethylcyclohexanone were also evaluated in the way previously described. The internal standard, ethyl benzoate, was weighed into the quenched reaction mixtures. A 20 foot 5% Carbowax column with chromosorb G-NAW (Chemical Research Services, Inc.) packing was used for the glpc separations. The flow rate of He was 60 cc per minute and the oven temperature was 135°C. All other conditions were the same as those for 2-methylcyclohexanone. Under these conditions the

Table 1. Reduction of 2-Methylcyclohexanone by Bis(dialkylamino)- and Bis(diarylamino)alanes in Benzene, Tetrahydrofuran, and Diethyl Ether

Reducing Agent	Solvent	Unreacted Ketone	Axial Alcohol	Equatorial Alcohol	Conversion	Yield
$(Et_2N)_2AlH$	Benzene	23	54	46	77	100
	THF	39	50	50	58	97
	Et_2O	21	53	47	63	84
$(i\text{-}Pr_2N)_2AlH$	Benzene	38	62	38	48	86
	THF	42	60	40	43	85
	Et_2O	44	67	33	48	92
$(Me_3N)AlH_3$	Benzene	0	38	62	100	100
	THF	0	39	61	100	100
	Et_2O	0	39	61	100	100
$(Ph_2N)_2AlH$	Benzene	65	63	37	29	94
	THF	59	70	30	30	89
	Et_2O	61	66	34	32	93
AlH_3	THF	0	36	64	88	88
$LiAlH_4$	THF	0	24	76	102	102

retention times for 3,3,5-trimethylcyclohexanone was 8 minutes. The retention tims for the axial and equatorial alcohols were 12 1/2 and 14 minutes respectively. The retention time for the internal standard was 25 minutes. The response ratios were essentially one to one on a molar scale. Each of the compounds in the organic layer of the reaction mixture separated very well and the peak areas were easily measured using a planimeter. The results of these reductions are found in Table 2.

The results in Table 2 show about the same percentage of axial alcohol regardless of the nature of the reducing agent. It appears that the axial methyl group at the 3 carbon on the ketone is the dominant factor which causes much more equatorial attack at the carbonyl. Therefore, the ketone appears very insensitive to the nature of the reducing agent as far as stereoselectivity is concerned.

Much of the large amounts of unreacted ketone was found to be a result of enolization.

The reductions of 4-t-butylcyclohexanone were run as previously described. The internal standard 3,3,5-trimethylcyclohexanone was weighed into the quenched reaction mixtures. The same separation column was used for 4-t-butylcyclohexanone as for the separations in the 3,3,5-trimethylcyclohexanone reductions. The flow rate of He was 60 cc per minute. The oven temperature was 135°C. All other conditions were the same as those used in the previous analyses.

Under these conditions the retention time for 4-t-butylcyclohexanone was 23 minutes. The retention times for the axial and equatorial alcohols were 27 and 30 minutes, respectively. The retention time for the internal standard was 8 minutes. The separations were excellent and

Table 2. Reduction of 3,3,5-Trimethylcyclohexanone by Bis-(dialkylamino)- and Bis(diarylamino)alanes in Benzene, Tetrahydrofuran and Diethyl Ether

Reducing Agent	Solvent	Unreacted Ketone	Axial Alcohol	Equatorial Alcohol	Conversion	Yield
$(Et_2N)_2AlH$	Benzene	30	73	27	57	87
	THF	45	78	22	55	100
	Et_2O	31	75	25	63	94
$(i\text{-}Pr_2N)_2AlH$	Benzene	41	77	23	45	86
	THF	36	79	21	62	98
	Et_2O	43	79	21	54	97
$(Me_3N)AlH_3$	Benzene	0	80	20	103	103
	THF	0	80	20	100	100
	Et_2O	0	84	16	107	107
$(Ph_2N)_2AlH$	Benzene	82	77	23	23	105
	THF	80	86	14	21	101
	Et_2O	55	82	18	35	90
AlH_3	THF	0	84	16	93	93
$LiAlH_4$	THF	0	76	24	102	102

and the peak areas were easily measured by use of a planimeter. The response ratios were essentially one to one on a molar scale. The results of the reductions are found in Table 3.

The results in Table 3 showed that the reduction of 4-t-butylcyclohexanone is relatively insensitive to the nature of the reducing agent or the solvent except when $(Ph_2N)_2AlH$ is the reducing agent. In these reductions a much smaller percentage of the axial alcohol was formed than in the previous cases just presented.

If a comparison is made between the results obtained in the reductions of 2-methylcyclohexanone and those of 4-t-butylcyclohexanone, one can see that there was a much greater percentage of equatorial alcohol formed in the 4-t-butylcyclohexanone experiments. One would expect the reduction of 2-methylcyclohexanone would yield similar percentage equatorial alcohol compared to 4-t-butylcyclohexanone. This expectation should have occurred if the ketone is in the chair form with the 2-methyl group equatorial. This conformation would afford little steric interaction to attack on the carbonyl group by the hydride from the axial side. A similar lack of interaction would be expected in the 4-t-butylcyclohexanone reductions. However, the experiments showed that there must be some interaction either steric or otherwise that caused a major amount of apparent equatorial attack on 2-methylcyclohexanone by the hydrides.

It is possible that 2-methylcyclohexanone reacts at a faster rate in another conformation such as shown in Figure 1. When 2-methyl-

Table 3. Reduction of 4-t-Butylcyclohexanone by Bis(Dialkylamino)- and Bis(diarylamino)alanes in Benzene, Tetrahydrofuran and Diethyl Ether

Reducing Agent	Solvent	Unreacted Ketone	Axial Alcohol	Equatorial Alcohol	Conversion	Yield
$(Et_2N)_2AlH$	Benzene	38	25	75	47	85
	THF	51	20	80	32	83
	Et_2O	53	22	78	35	88
$(i\text{-}Pr_2N)_2AlH$	Benzene	56	25	75	30	86
	THF	60	20	80	27	87
	Et_2O	70	27	73	33	103
Me_3NAlH_3	Benzene	0	19	81	99	99
	THF	0	19	81	97	97
	Et_2O	0	20	80	95	95
$(Ph_2N)_2AlH$	Benzene	75	47	53	11	86
	THF	72	44	56	13	85
	Et_2O	77	41	59	13	90
AlH_3	THF	0	13	87	100	100
$LiAlH_4$	THF	trace	7	93	97	97

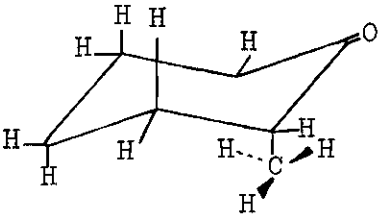


Figure 1

cyclohexanone reacted as the conformer shown in Figure 1, it would be expected to show a large percentage of apparent equatorial attack by the hydride. This would mean that attack actually occurred axially but when the final product "flipped" to the most stable conformer the resulting product appeared to have been formed by equatorial attack. The methyl group axial (Figure 1) at the 2 position would presumably hinder equatorial attack on this conformer.

The reductions of camphor by the four hydrides $(Et_2N)_2AlH$, $(i\text{-}Pr_2N)_2AlH$, $(Ph_2N)_2AlH$ and Me_3NAlH_3 were also evaluated. Camphor is a rigid system and the reductions were sterically controlled.

The gas chromatographic conditions used for the separation of the components of the reaction mixture were the same as those used for 4-t-butylcyclohexanone. Under these conditions the retention time for camphor was 15 minutes. The retention times for the endo and exo alcohols were 24 and 28 minutes, respectively. The retention time for the internal standard (3,3,5-trimethylcyclohexanone) was 8 minutes.

The separations were excellent and the peak areas were easily measured. The response ratios were one to one on a molar scale. The results of these reductions are shown in Table 4.

Table 4. Reduction of Camphor by Bis(dialkylamino)- and Bis(diarylamino)alanes in Benzene, Tetrahydrofuran and Diethyl Ether

Reducing Agent	Solvent	Unreacted Ketone	Exo Alcohol	Endo Alcohol	Conversion	Yield
$(Et_2N)_2AlH$	Benzene	83	70	30	20	103
	THF	77	71	29	21	98
	Et_2O	92	71	29	13	105
$(i\text{-}Pr_2N)_2AlH$	Benzene	39	78	22	46	85
	THF	42	82	18	50	92
	Et_2O	43	77	23	56	99
Me_3NAlH_3	Benzene	0	70	30	96	96
	THF	0	77	23	89	89
	Et_2O	0	76	24	105	105
$(Ph_2N)_2AlH$	Benzene	86	78	22	13	99
	THF	70	71	29	33	103
	Et_2O	64	86	14	29	93
AlH_3	THF	0	87	13	89	89
$LiAlH_4$	THF	0	90	10	97	97

In Table 4 the data shows camphor to be relatively insensitive to the nature of the reducing agent.

In each reaction involving the secondary amine alanes the percentage of unreacted ketone was considerable indicating that the steric interference to the hydrides was great in these reductions and the reaction rates were slowed down considerably. Also, there occurred some enolization and upon hydrolysis the ketone was regenerated.

Norcamphor was reduced by each of the hydrides being evaluated. All conditions for gas chromatographic analysis were the same as for camphor. The same column and the same internal standard was used. Under these conditions the retention time for norcamphor was 10 minutes. The retention time for the endo and exo-alcohols were 14 and 15 1/2 minutes, respectively. The separations were very good and the peak areas were measured by a planimeter. The response ratios were essentially one to one on a molar scale. The results from these reductions are listed in Table 5.

The reductions of norcamphor (Table 5) also seemed to be insensitive to both solvent and the nature of the reducing agent. Never was the percentage of the exo-alcohol formed greater than 13% and never lower than 4%.

When a comparison was made between the reductions of camphor and norcamphor, it was found that a much greater amount of reduction of the starting material occurred with norcamphor. This fact would indicate a great amount of steric hindrance to both exo and endo attack in the reduction of camphor.

It appeared that in the reductions of camphor and norcamphor steric

Table 5. Reduction of Norcamphor by Bis(dialkylamino)- and Bis(diarylamino)alanes in Benzene, Tetrahydrofuran and Diethyl Ether

Reducing Agent	Solvent	Unreacted Ketone	Exo Alcohol	Endo Alcohol	Conversion	Yield
$(Et_2N)_2AlH$	Benzene	24	13	87	68	92
	THF	26	11	89	60	86
	Et_2O	29	10	90	59	88
$(i\text{-}Pr_2N)_2AlH$	Benzene	21	5	95	72	93
	THF	23	10	90	69	92
	Et_2O	22	7	93	67	89
Me_3NAlH_3	Benzene	0	8	92	86	86
	THF	0	7	93	110	110
	Et_2O	0	6	94	82	82
$(Ph_2N)_2AlH$	Benzene	22	5	95	69	91
	THF	23	4	96	70	93
	Et_2O	26	5	95	66	92
AlH_3	THF	0	6	94	90	90
$LiAlH_4$	THF	2	9	91	90	90

interference was the most predominant force guiding the stereochemical course of reduction. In each instance involving the reduction of camphor or norcamphor the major product was formed by attack from the least hindered side of the carbonyl.

Enolization Experiments

Two 50 milliliter reaction flasks were set up equipped with 3/8 inch magnetic stirring bars and 24/40 standard tapered ground glass stoppers equipped with 3-way stopcocks. These flasks were flamed 3 times under vacuum and then purged with dry nitrogen. During the addition of the reactions and during reaction the system was kept under a positive pressure of dry nitrogen.

The hydride used in these reductions was $(i\text{-}Pr_2N)_2AlH$. 3.1 milliliters of a 0.98 molar solution of the hydride in benzene was added by syringe to each of the flasks. 10 milliliters of dry solvent were added by syringe to the hydride in the flask. Benzene was used as solvent when camphor was reduced and THF was the solvent when 4-t-butylcyclohexanone was reduced. After addition of the solvent 10 milliliters of the 0.2 molar ketone solutions in the respective solvents were added to the reaction solution while stirring was in progress.

These reductions were allowed to run for 4 days. After four days a 2 milliliter aliquot of each solution was removed, hydrolyzed by saturated NH_4Cl solution and analyzed by gas chromatography. The results of these analyses are found in Table 6.

Also, after the same 4 days an additional 1 milliliter of the 0.98 molar solution of the hydride was added to each reaction flask and

Table 6. Determination of the Amount of Enolization in the Reduction of Camphor and 4-t-Butylcyclohexanone by $(i\text{-}Pr_2N)_2AlH$

	4 Days	6 Days
Camphor	40% unreacted ketone	40% unreacted ketone
	60% conversion	60% conversion
	74% endo alcohol	75% endo alcohol
	26% exo alcohol	25% exo alcohol
4-t-Butylcyclohexanone	60% unreacted ketone	58% unreacted ketone
	40% conversion to alcohols	42% conversion to alcohols
	74% equatorial attack	78% equatorial attack
	26% axial attack	22% axial alcohol

reaction was continued for another 2 days. At this time the entire solution was hydrolyzed and analyzed. These results can also be found in Table 6.

The data in Table 6 shows conclusively that enolization occurred, because the percentages shown for both analyses are essentially the same and if enolization did not occur the 2nd analysis should have shown less unreacted ketone than the 1st analysis.

The reductions of the five representative ketones were carried out using bis(2,6-dimethylpiperidino)alane as the reducing agent. These reductions were carried out only in benzene. The same conditions were used in these reductions as in the previous ones. These reductions were very slow or a large amount of enolization occurred because the largest percentage of reduction products from any of the ketones was 8%. The results of these reductions can be found in Table 7.

If these results (Table 7) are compared to previous reductions using the other hydrides evaluated, one can see that the reductions seem to be insensitive to the size of the hydride since this very large hydride gave almost the same percentages of the respective alcohols as the smaller hydrides.

Concentration Experiments

In order to examine the effect of concentration on the stereoselectivity of these reducing agents being evaluated, some reductions were run at concentrations of .01 molar in hydride and .0067 molar in substrate. Some reductions were also run at concentrations of .001 molar in hydride and .00067 in substrate. These molar ratios allowed the 1.5

Table 7. Reductions of Cyclic Ketones Using Bis(2,6-dimethylpiperidino)alane

2-Methylcyclohexanone	3,3,5-Trimethylcyclohexanone
95% unreacted ketone	93% unreacted ketone
5% conversion to alcohols	7% conversion to alcohols
60% axial alcohol	80% axial alcohol
40% equatorial alcohol	20% equatorial alcohol
4-t-Butylcyclohexanone (Benzene Solution)	**4-t-Butylcyclohexanone (THF Solutions)**
94% unreacted ketone	95% unreacted ketone
6% conversion	5% conversion to alcohols
30% axial alcohol	29% axial alcohol
70% equatorial alcohol	71% equatorial alcohol
Camphor	**Norcamphor**
93% unreacted ketone	92% unreacted ketone
7% conversion to alcohols	8% conversion to alcohols
65% exo alcohol	90% endo alcohol
35% endo alcohol	10% exo alcohol

to 1 ratio of hydride to substrate to be maintained in the concentration studies.

The solution of the hydride [$(i\text{-}Pr_2N)_2AlH$] was prepared in dry benzene by adding the appropriate amount of a 0.98 molar benzene solution of $(i\text{-}Pr_2N)_2AlH$ to a 100 milliliter boiling flask, which had been flame dried under vacuum and equipped with 24/40 standard tapered ground glass stopper equipped with a 3-way stopcock. Then an amount of benzene was added by syringe to arrive at the proper concentration. All operations were carried out under a positive dry nitrogen pressure.

The reaction flasks, two 50 milliliter boiling flasks equipped with 3/8 inch stirring bars and 24/40 ground glass standard tapered stoppers equipped with 3-way stopcocks were flame dried under vacuum before addition of the reactants. The reactants were added by first adding the hydride and then the substrate solution. The substrate solution had also been prepared to the molar specifications which have been previously described. The reactions were allowed to run for 2 hours and were quenched in the usual way.

As the data in Table 8 shows, there is little variation in the stereoselectivity with concentration.

Temperature Experiments

The reduction of camphor and 3,3,5-trimethylcyclohexanone was carried out in Et_2O solution at -80°C. The hydride used was $(i\text{-}Pr_2N)_2AlH$.

The reductions were carried out by setting up two 50 milliliter boiling flasks equipped with 3/8 inch stirring bars and 24/40 standard tapered ground glass stoppers equipped with 3-way stopcocks. These flasks

Table 8. Effect of Concentration on Stereoselectivity in the Reduction of Cyclic and Bicyclic Ketones with $(i\text{-}Pr_2N)_2AlH$

	.01 Molar	.001 Molar
3,3,5-Trimethylcyclohexanone	57% conversion to alcohols	8% conversion to alcohols
	82% axial alcohol	85% axial alcohol
	18% equatorial alcohol	15% equatorial alcohol
Camphor	59% conversion to alcohols	6% conversion to alcohols
	78% endo alcohol	84% endo alcohol
	22% exo alcohol	16% exo alcohol

were flame dried under vacuum and allowed to cool to room temperature. The flasks were then cooled to -80°C in a dry ice acetone bath. 3 milliliters of a 1 molar Et_2O solution of $(i\text{-}Pr_2N)_2AlH$ was then added under positive dry nitrogen pressure. A 10 milliliter aliquot of a 0.2 molar Et_2O solution of the respective ketone was added to the reaction flasks. The reactions were allowed to stir for 2 hours. The data from these experiments can be found in Table 9.

The lower temperature seemed to have little effect on the stereoselectivity of the reducing agent. However, the decrease in temperature did slow the reaction down considerably. This difference in the speed of the reaction can be assumed, because the difference in the amount of unreacted ketone at 0°C (Tables 2 and 6) and at -80°C (Table 9) was very significant.

Me_3NAlH_3 Reactivity Experiments

Two reduction experiments were carried out in the previously described general manner. The only difference being that in one instance 1 millimole of Me_3AlH_3 was allowed to react with 3 millimoles of 3,3,5-trimethylcyclohexanone and in the other instance 1 millimole of Me_3NAlH_3 was allowed to react with 1 millimole of the same ketone. The purpose of these experiments was to determine if the reaction at 1:3 ratio is more selective than the reaction at 1:1 ratio. If the reduction proceeds by Scheme I when the ratio of hydride substrate is 1:3, then a difference should be seen in the stereoselectivity of the reduction, as the reaction proceeds.

Table 9. The Effect of Low Temperature (-80°C) on the Stereochemistry of Cyclic and Bicyclic Ketone Reductions by $(i\text{-}Pr_2N)_2AlH$

Ketone Studied	Recovered Ketone (%)	Conversion (%)	Axial Alcohol (%)	Equatorial Alcohol (%)
3,3,5-Trimethyl-cyclohexanone	83	17	79	21
Camphor	76	24	82 (exo)	18 (endo)

$$AlH_3NR_3 + R_2C{=}O \rightarrow (R_2\text{-}\overset{H}{C}\text{-}O)AlH_2 \xrightarrow{R_2C=O} (R_2C\text{-}O)_2AlH \xrightarrow{R_2C=O} (R_2\text{-}\overset{H}{C}\text{-}O)_3Al$$

Scheme I

However, if in each step the intermediate disproportionates, the reducing species would be the same in each step and no difference would have occurred in the ratio of the axial and equatorial alcohols as the reaction proceeds. On the other hand, if little difference in the product ratio is observed as the reaction proceeds, it could be that the stereochemistry is insensitive to the steric requirement of the hydride.

No difference in the ratio of axial:equatorial alcohol was observed when the hydride:ketone ratio varied from 1:1 to 1:3 (Table 10).

Functional Group Reductions

The organic functional compounds reduced in this study were an aldehyde, an organic acid, an ester, an acid chloride, an amide, an epoxide, an alkyl halide and an alkene. These reductions were evaluated in benzene solution. The hydrides used for these reductions were the same as those used in the stereoselective reductions. The hydrides were prepared by the same procedure as previously described and were stored in benzene. Bis(diphenylamino)alane was stored as the solid under vacuum in the glove box.

Solutions of the compounds (0.2 molar) to be reduced were prepared in benzene. The preparation of the solution was the same as that discussed for the ketones in the stereoselective reductions. The reductions were carried out under the same conditions described earlier for

Table 10. Effect of Stoichiometry on the Stereochemistry of Reduction of 3,3,5-Trimethylcyclohexanone by Me_3NAlH_3

Hydride:Substrate	Conversion to Alcohols (%)	Axial Alcohol (%)	Equatorial Alcohol (%)
1:1	100	80	20
1:3	100	80	20

the stereoselective reduction studies. The ratio of hydride to substrate was 1.5 millimoles to 1 millimole respectively for all reductions except those of benzoic acid when a large excess (4 millimoles of hydride to 1 millimole of substrate) of reducing agent was used. The reductions were carried out for 2 hours at room temperature. All reaction solutions, except those of benzoyl chloride, were quenched in the usual manner by addition of 1 milliliter of saturated NH_4Cl solution. When benzoyl chloride was reduced the reaction solution was quenched first by addition of 100% ethanol to form ethyl benzoate from the unreacted acid chloride. This solution was then quenched with 1 ml of saturated NH_4Cl solution. The unreacted acid chloride appeared in the gas chromatograph analysis as ethyl benzoate.

The internal standards were added to the solutions and the solutions were analyzed by gas chromatography. The conditions for analysis are found in Table 11.

During the course of the functional group study an interesting development occurred. In all reductions involving a carbonyl functional group the major product was a tertiary amine. This result was an unexpected occurrence and it was necessary to provide satisfactory identification of these products. An example of the preceeding reaction can be represented by the following equation.

$$(NR_2)_2AlH + PhCHO \xrightarrow{Ph} \underset{\text{(major product)}}{PhCH_2NR_2}$$

The amine formed, when bis(diethylamino)alane is the reducing agent, is

Table 11. Conditions of Analysis

Compound Reduced	Column Used For Separation	Oven Temp. °C	Internal Standard
styrene oxide	5 ft. 5% Carbowax	125°	trans-2-methylcyclohexanone
styrene	"	90°	n-hexanol
ethyl benzoate	"	125°	decyl alcohol
benzoic acid	"	125°	decyl alcohol
benzoylchloride	"	125°	decyl alcohol
benzaldehyde	"	125°	ethyl benzoate
N,N-dimethylbenzamide	20 ft 5% Carbowax	125°	3,3,5-trimethylcyclohexanone
1-phenyl-2-chloro-ethane	6 ft. 10% diisodeal thiolate	150°	2-methylcyclohexanone

diethylbenzylamine. Diisopropylbenzylamine was formed when bis(diisopropylamino)alane was the reducing agent and diphenylbenzylamine was formed when bis(diphenylamino)alane was the reducing agent.

Identification of the Tertiary Amines

The separation of the amine from the reaction solution was made by first acidifying the solution with 10% HCl solution. The water layer was separated using a separatory funnel, and was then made basic by the addition of a 1 molar solution of NaOH. The amine precipitated from solution. Diethyl ether was then added to the basic solution and the amine was extracted into the organic layer. The ether layer was then separated using a separatory funnel, and the ether was allowed to evaporate in the hood. The solid tertiary amine remained after evaporation of the solvent.

Mass spectra were obtained for each amine and nmr spectra were obtained for both diethylbenzylamine and diisopropylbenzylamine. A retention time for diphenylbenzylamine was found on the gas chromatograph and the major product in the reductions using bis(diphenylamino)alane had the same retention time under the same conditions.

The data for these identifications can be found in the following paragraphs.

Data for Identification of Diethylbenzyl Amine

The mass spectrum for this compound had a molecular ion peak at 163. A large peak was shown at $(M^+ - 15)$ which would represent the loss of one of the methyl groups. An ion peak was found at $(M^+ - 72)$ which corresponds to the benzyl ion. These were the predominant peaks observed.

The nmr spectrum for this amine was run in CS_2 and TMS was used as a reference. This spectrum showed a triplet at 8.89τ for the methyl protons, a quartet at 6.63τ for the $-CH_2-$ protons, the aromatic protons were observed at 2.83τ, and the singlet for the benzyl protons is hidden under the quartet at approximately 6.7τ. The two spectra clearly identify the compound as diethylbenzyl amine.

Data for the Identification of Diisopropylbenzyl Amine

The mass spectrum for this compound had a very strong molecular ion was at ($M^+ = 191$). The ion peak at $M^+ - 15$ is due to the loss of a methyl group. Also, a very large peak was found at ($M^+ - 100$) which is caused by the loss of the diisopropyl amino group. These were by far the largest and most prominent peaks to appear in the spectrum. The nmr of diisopropylbenzyl amine was also run in CS_2 using TMS as a reference. There appeared in the spectrum a doublet at 9.0τ (methyl group protons), a multiplet at 7.0τ (single proton on the center carbon of the isopropyl groups), a singlet at 6.4τ (methylene protons) and the aromatic protons absorbed at 2.78τ.

The mass spectral and nmr spectra clearly identified the compound as diisopropylbenzyl amine.

Data for the Identification of Diphenylbenzyl Amine

A difficulty arose in the identification of this compound. When the separation procedures were used for the reaction solutions in which bis(diphenylamino)alane had been used as the reducing agent, the diphenylamine formed in the reaction always contaminated the tertiary amine becuase diphenylamine was also a solid. However, even with this contamina-

tion the mass spectrum of the solid mixture showed a molecular ion at ($M^+ = 259$). This is the exact molecular weight of the tertiary amine. Also, an ion was shown at ($M^+ - 168$) which indicated the presence of the benzyl ion. The retention time for the major product in the reaction solution was compared to that of the known compound under the same conditions. The retention times were found to be the same. The gas chromatographic conditions were the following: oven temperature 170°C, flow rate 60 cc per minute, injection port temperature 260°C, detector temperature 290°C, and bridge power 150 milliamps. Six foot matched SE-30 columns were used for the separations. The retention time was 7 1/2 minutes. This data clearly indicates the presence of diphenylbenzyl amine.

Tables 9 through 11 contain the data for functional group reduction.

Attempted Reduction of Styrene and 1-Phenyl-2-Chloroethane

No reduction of styrene or 1-phenyl-2-chloroethane was observed using any of the $(R_2N)_2AlH$ compounds employed in this study.

CHAPTER III

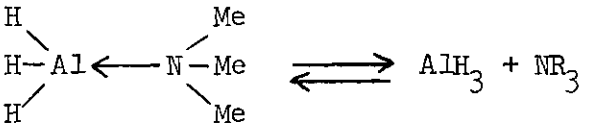
DISCUSSION AND RESULTS

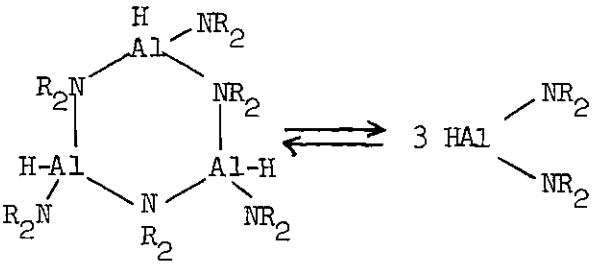
Discussion of Stereoselective Reductions

Stereoselective reduction of ketones is a topic which has aroused great interest in recent years.[13,23-25] Both the theoretical interest of these reductions,[23,24] and the high potential utility of a reducing agent of exceptional selectivity[27] have fed this interest. Dauben and coworkers[24] developed the concept of steric approach control and product development control to explain stereochemical results. Cherest and Felkin,[23] more recently proposed that the balancing of torsional strain and steric strain causes the results observed in cyclic and bicyclic ketones. Both concepts tend to explain the results of hydride reduction of ketones in terms of factors operating in the ketones alone; results in this and other investigations have been obtained which cannot be explained satisfactorily by either concept.

The fact that reductions of cyclohexanones with metal hydrides are much more sensitive to the nature of the particular hydride in the case of a ketone bearing a substituent in the 2-position as in contrast to the 3- or 4-position indicates that torsional effects may be more important than steric effects, and also that the reaction may take place by complexation of the hydride with the ketone prior to reduction. [Note: Rapid reaction of AlH_3NMe_3 compared to $HAl(NR_2)_2$ compounds.] In AlH_3NMe_3 reduction, NMe_3 can be easily displaced by the basic ketones whereas $HAl(NR_2)_2$ compounds are much less capable of being complexed by ketones

since stable back bonded associated species are formed. The aluminum atom is more electron deficient in $HAl(NR_2)_2$ compounds than in AlH_3NR_3 compounds.





The aluminum atom is less electrophilic in $HAl(NR_2)_2$ compounds than in AlH_3NR_3 due to back bonding in the $HAl(NR_2)_2$ compounds.

The bis(dialkylamino)- and bis(diarylamino)alanes have been shown in this study to be reasonably good reducing agents. However, the selectivity of these hydrides does not appear to change greatly with increasing size of the dialkyl- or diarylamino group. A possible explanation for this behavior could be that the size of the hydride is not of great significance to the stereochemistry of the reaction. Other factors may have much greater effects than the size of the hydride.

It has also been found in this laboratory that alkoxyalanes[14] reduce ketones in a non-selective way on the basis of steric requirement of the alkoxy group. The insensitivity of the stereochemistry to the steric requirement of the hydride suggests that possibly the hydride ion is transferred to the carbonyl group from a greater distance in the

transition state (early transition state) or that the torsional strain involved in equatorial attack does not change much as the steric requirement of the hydride increases.

In Table 1 it can be seen that the larger more hindered hydrides, $(i\text{-}Pr_2N)_2AlH$ and $(Ph_2N)_2AlH$, do show a little more selectivity in the reduction of 2-methylcyclohexanone than does $(Et_2N)_2AlH$. The larger hydrides yield a greater percentage of the product formed from equatorial attack on the chair conformation of the 2-methylcyclohexanone.

The $(Me_3N)AlH_3$ reacted with 2-methylcyclohexanone to yield essentially the same percentage of axial and equatorial alcohols as AlH_3. This result would tend to make one suspect that the reducing using $(Me_3N)AlH_3$ proceeds through a similar mechanism as when AlH_3 is the reducing agent.

In the reduction of 3,3,5-trimethylcyclohexanone (Table 2) both $(Et_2N)_2AlH$ and $(i\text{-}Pr_2N)_2AlH$ react to give very similar results. The percentages of axial and equatorial alcohols are quite similar when either of these two reducing agents are used. Also, the amount of unreacted ketone remaining is quite similar. This characteristic would indicate that in these reductions the steric interactions involved, when either the $(Et_2N)_2AlH$ or $(i\text{-}Pr_2N)_2AlH$ are used, are very similar. The yield and conversion are also quite similar. The compound, $(Ph_2N)_2AlH$, is a little more selective in the reduction of 3,3,5-trimethylcyclohexanone, however, this reaction may be considerably slower than the ones involving the other hydrides. The conversion using $(Ph_2N)_2AlH$ is very low which would suggest either a slow reaction or a greater amount of enolization occurring. Table 2 indicates that the solvent seems to have little effect

on the selectivity of the reducing agents. Also, again as in Table 1, $(Me_3N)AlH_3$ appears to react to give essentially the same ratio of alcohols as AlH_3.

As shown by the data in Tables 1 and 2, the axial methyl group at the 3-position in 3,3,5-trimethylcyclohexanone has a considerable effect in reducing axial attack on the carbonyl group. The yield of axial alcohol when 3,3,5-trimethylcyclohexanone is reduced is considerably greater than when 2-methylcyclohexanone is reduced.

The reductions of 4-t-butylcyclohexanone, Table 3, by the respective hydrides showed little difference in selectivity comparing $(Et_2N)_2AlH$ and $(i\text{-}Pr_2N)_2AlH$. However, the $(Ph_2N)_2AlH$ gave a much greater percentage of axial alcohol than either of the other two bis(dialkylamino)alanes. This difference in selectivity could indicate that the larger hydride experienced some difficulty attacking the carbonyl group axially. Unfortunately, the conversion is quite small when $(Ph_2N)_2AlH$ is the reducing agent. This lack of conversion could be caused by a much slower reaction or an increase in enolization.

Table 4 indicates that the reduction of camphor is sterically controlled. The exo alcohol is the major product formed in each reduction. There appears to be little sensitivity on the part of the ketone to the nature or size of the reducing agent. The conversion in general seems to be considerably less with camphor than with the other ketones, a result which is consistent with the much greater hindrances of the camphor compared to the other ketones used in the study. Also, the enolization experiments carried out show that in the reductions of camphor and 3,3,5-trimethylcyclohexanone a larger amount of enolization occurs.

The hydride, Me_3AlH_3, reacts with camphor to give essentially the same percentage of exo alcohol as $(Et_2N)_2AlH$, $(i\text{-}Pr_2N)_2AlH$ and $(Ph_2N)_2AlH$. However, Me_3AlH_3 converts the ketone completely to the alcohols indicating a much faster rate of reduction than with the $(R_2N)_2AlH$ compounds.

The reductions of norcamphor (Table 5) show considerably more conversion to the alcohols compared to the reduction of camphor. This increase in conversion indicates less steric hinderance to attack by the hydrides in the case of norcamphor which is to be expected. Also less enolization occurs when norcamphor is reduced with the hydrides being studied. In each reduction of norcamphor the endo-alcohol was formed in an approximate ratio of 9 to 1 over the exo alcohol indicating that exo attack on the molecule is much less hindered than endo attack.

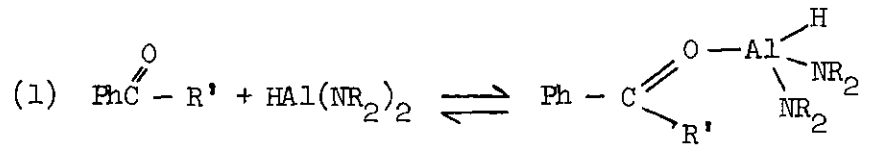
The enolization experiments (Table 6) indicate that enolization does occur when $(i\text{-}Pr_2N)_2AlH$ is used as the reducing agent. Due to the similarities in the conversion, it could be assumed that enolization also occurs when any of these bis(dialkylamino)- or bis(diarylamino)alanes are used as reducing agents for the ketones studied. Enolization, therefore, is probably a major reason that complete conversion to the alcohols does not occur.

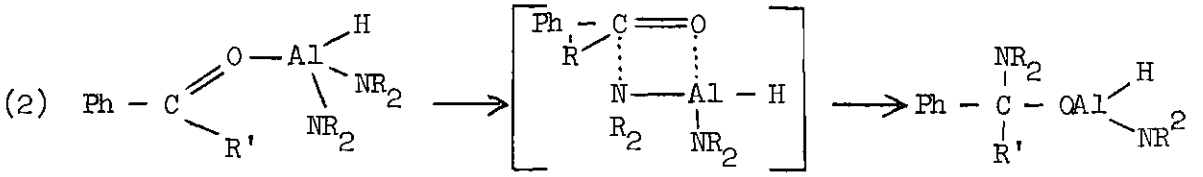
Discussion of Functional Group Reduction

Tables 12 through 17 reveal very little with respect to expected products except in the formation of tertiary amines as the major product in the reduction of benzaldehyde, benzoic acid, benzoyl chloride, and ethyl benzoate. In each of these cases the reaction probably proceeds

through similar intermediates.

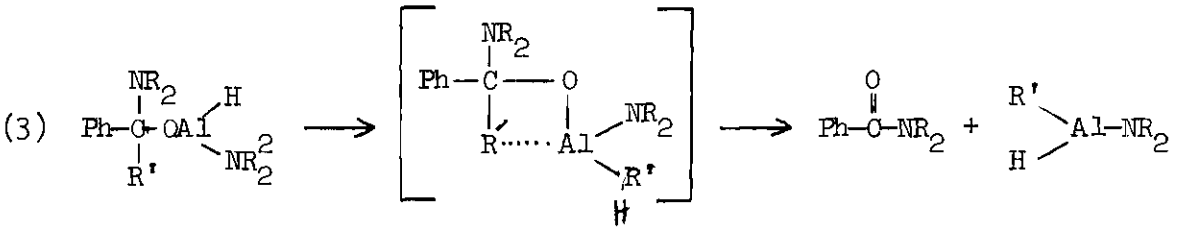
Since reduction of N,N-dimethylbenzamide produces dimethylbenzylamine as the major product, it would not be unreasonable to assume that the reductions of the other carbonyl compounds (e.g., benzaldehyde, benzoic acid, etc.) may first react to give the amide which is then reduced to the tertiary amine. The following mechanism can be written.



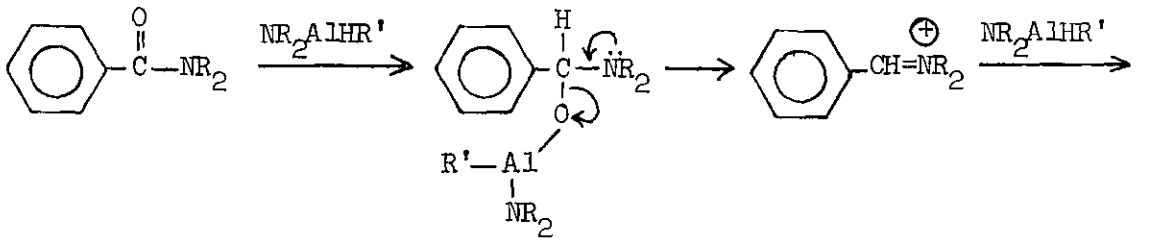


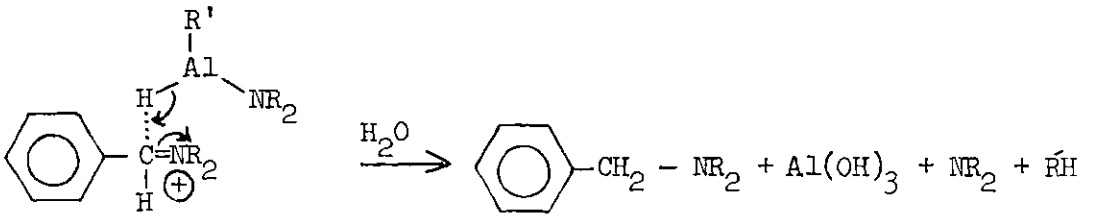
R = Et, i-Pr, Ph

R' = H, OEt, Cl, OH



If the mechanism proceeds through the amide, then the hydride (H_2AlNR_2) could reduce the amide to the amine as reported previously for the reduction of N,N-dimethylbenzamide by AlH_3.

(4) 

(5) 

The reaction of $HAl(NR_2)_2$ compounds with aldehydes to form tertiary amines could provide an important new route to tertiary amines. The reaction is somewhat described as an internal reductive alkylation.

The bis(dialkylamino)alanes and bis(diarylamino)alanes could also be used to selectively reduce other functional groups in the presence of alkenes and alkyl halides without affecting the alkene or alkyl halide function.

Bis(dialkylamino)alanes and bis(diarylamino)alanes were found to be relatively good reducing agents. Although some of the experimental results obtained during this study could be pursued in greater detail, the major objective of the study was accomplished. The purpose of this

study was to evaluate $HAl(NR_2)_2$ compounds as reducing agents in terms of stereoselectivity and functional group selectivity. The results reported herein show that this purpose was accomplished.

Table 12. Reductions of Benzaldehyde

Reducing Agent	Time Hrs.	Results
$(Et_2N)_2AlH$	2	38% unreacted substrate
	24	49% 3° amine formed
		12% benzyl alcohol
$(Et_2N)_2AlH$	24	15% unreacted substrate
		46% 3° amine
		18% benzyl alcohol
$(ipr_2N)_2AlH$	2	0% recovery of substrate
		74% 3° amine
		27% benzyl alcohol
$(ipr_2N)_2AlH$	24	0% recovery of substrate
		70% 3° amine
		29% benzyl alcohol
$(Ph_2N)_2AlH$	2	0% recovery of substrate
		70% conversion to 3° amine
		27% conversion to benzyl alcohol
$(Ph_2N)_2AlH$	24	0% recovery of substrate
		75% conversion to 3° amine
		33% conversion to benzyl alcohol
Me_3NAlH_3	2	0% recovery of substrate
		100% benzyl alcohol
Me_3NAlH_3	24	0% recovery of substrate
		100% benzyl alcohol

Table 13. Reductions of Benzoic Acid

Reducing Agent	Time Hrs.	Results
$(Et_2N)_2AlH$	2	50% unreacted substrate 48% 3° amine 2% benzaldehyde
$(Et_2N)_2AlH$	24	37% unreacted substrate 51% 3° amine 7% benzaldehyde 2% benzyl alcohol
$(ipr_2N)_2AlH$	2	38% unreacted substrate 48% 3° amine trace benzaldehyde 14% benzyl alcohol
$(ipr_2N)_2AlH$	24	26% unreacted substrate 60% 3° amine 2% benzaldehyde 12% benzyl alcohol
$(Ph_2N)_2AlH$	2	60% unreacted substrate 35% 3° amine 5% benzyl alcohol trace benzaldehyde
$(Ph_2N)_2AlH$	24	44% unreacted substrate 48% 3° amine 8% benzyl alcohol
Me_3NAlH_3	2	89% benzyl alcohol 2% benaldehyde
Me_3NAlH_3	24	94% benzyl alcohol 4% benzaldehyde

Table 14. Reductions of Ethylbenzoate

Reducing Agent	Time Hrs.	Results
$(Et_2N)_2AlH$	2	29% recovered substrate 42% 3° amine 15% benzyl alcohol
$(Et_2N)_2AlH$	24	0% recovered substrate 80% 3° amine 11% benzyl alcohol
$(ipr_2N)_2AlH$	2	27% recovered substrate 48% 3° amine 24% benzyl alcohol
$(ipr_2N)_2AlH$	24	12% recovered substrate 63% 3° amine 20% benzyl alcohol
$(Ph_2N)_2AlH$	2	90% recovered substrate no conversion
$(Ph_2N)_2AlH$	24	66% recovered substrate 23% 3° amine 11% benzyl alcohol
$(Me_3N)AlH_3$	2	58% recovered substrate 37% benzyl alcohol
$(Me_3N)AlH_3$	24	58% recovered substrate 47% benzyl alcohol
$(Me_3N)AlH_3$ excess	2	0% recovered substrate 97% benzyl alcohol

Table 15. Reductions of Benzoylchloride

Reducing Agent	Time Hrs.	Results
$(Et_2N)_2AlH$	2	30% unreacted substrate 50% 3° amine 6% benzyl alcohol traces of benzaldehyde
$(Et_2N)_2AlH$	24	10% unreacted substrate 59% 3° amine 15% benzyl alcohol
$(ipr_2N)_2AlH$	2	18% unreacted substrate 47% 3° amine 13% benzyl alcohol
$(ipr_2N)_2AlH$	24	16% unreacted substrate 57% 3° amine 27% benzyl alcohol
$(Ph_2N)_2AlH$	2	35% recovery of substrate 15% benzyl alcohol 46% 3° amine
$(Ph_2N)_2AlH$	24	18% recovered substrate 58% 3° amine 18% benzyl alcohol
Me_3NAlH_3	2	50% recovered substrate 42% benzyl alcohol 5% benzaldehyde trace of substrate
Me_3NAlH_3	24	81% benzyl alcohol 9% benzaldehyde

Table 16. Reductions of N,N-dimethylbenzamide

Reducing Agent	Time Hrs.	Results
$(Et_2N)_2AlH$	2	59% unreacted 34% N,N-dimethylbenzylamine 7% benzaldehyde
$(Et_2N)_2AlH$	24	48% unreacted 35% N,N-dimethylbenzylamine 17% benzaldehyde
$(ipr_2N)_2AlH$	2	27% unreacted 65% N,N-dimethylbenzylamine 8% benzaldehyde
$(ipr_2N)_2AlH$	24	17% unreacted 63% N,N-dimethylbenzylamine 19% benzaldehyde
$(Ph_2N)_2AlH$	2	85% unreacted 15% N,N-dimethylbenzylamine
$(Ph_2N)_2AlH$	24	57% unreacted 31% N,N-dimethylbenzylamine 12% benzaldehyde
$(Me_3N)AlH_3$	2	40% unreacted 50% N,N-dimethylbenzylamine 10% benzaldehyde
$(Me_3N)AlH_3$	24	82% N,N-dimethylbenzylamine 11% benzaldehyde

Table 17. Reductions of Styrene Oxide

Reducing Agent	Time Hrs.	Results
$(Et_2N)_2AlH$	2	58% recovered substrate 38% conversion to alcohols 24% conversion to ϕ-CHOH-CH_3=65% 14% conversion to ϕ-CH_2-CH_2OH=35%
$(Et_2N)_2AlH$	24	22% recovered substrate 69% conversion to alcohols 46% ϕCHOH-CH_3=67% 23% ϕCH_2-CH_2OH=33%
$(ipr_2N)_2AlH$	2	50% recovered substrate 42% conversion to alcohols 29% ϕ-CHOH-CH_3=68% 13% ϕ-CH_2-CH_2OH=32%
$(ipr_2N)_2AlH$	24	3% recovered substrate 86% conversion to alcohols 57% ϕCHOH-CH_2OH=66% 29% ϕCH_2-CH_2OH=34%
$(Ph_2N)_2AlH$	2	78% recovered substrate 15% conversion to alcohols 11% ϕ-CHOH-CH_3=73% 4% ϕ-CH_2-CH_2OH=27%
$(Ph_2N)_2AlH$	24	31% recovered substrate 62% conversion to alcohols 43% ϕ-CHOH-CH_3=69% 19% ϕ-CH_2-CH_2OH = 31%
Me_3NAlH_3	2	6% recovered substrate 94% conversion to products 57% ϕ-CHOH-CH_3=60% 37% ϕ-CH_2-CH_2OH=40%

Table 17. Reductions of Styrene Oxide (Continued)

Reducing Agent	Time Hrs.	Results
Me_3NAlH_3	24	no recovered substrate 87% conversion to products 52% $\phi CHOH\text{-}CH_3$ = 60% 35% ϕCH_2CH_2OH = 40%

CHAPTER IV

CONCLUSIONS

An extensive study of the reduction of five representative cyclic ketones was carried out. The reductions were carried out using bis(dialkylamino) and bis(diarylamino)alanes as the reducing agents. These hydrides had not previously been evaluated as reducing agents. The precursor to these hydrides [$AlH_3N(CH_3)_3$] was also evaluated as a reducing agent.

Each ketone was carefully selected so that the information gained from its reduction products could be meaningful. The ketones reduced were 2-methylcyclohexanone; 3,3,5-trimethylcyclohexanone, 4-t-butylcyclohexanone, camphor, and norcamphor. Each of these ketones presented different steric requirements and the reduction of each was hoped to give important information concerning the reducing capability of the hydrides.

The hydrides used in these reductions were bis(diethylamino)alane, bis(diisopropylamino)alane, bis(diphenylamino)alane, and the precursor to these, trimethylamine alane. Each of these hydrides have different steric requirements and provide important information concerning the reactivity of the hydrides as well as the stereochemistry of the reactions involved.

The effect of solvent in these reductions was also evaluated. The reductions were carried out in benzene, diethyl ether, and tetrahydrofuran. Each reduction reaction was carried out for two hours at 0°C when diethyl ether and tetrahydrofuran were the solvents. However, due to the

freezing point of benzene, the reductions in this solvent were carried out at room temperature for two hours.

The effect of concentration on stereochemistry was determined. These reactions were carried out only in benzene using 3,3,5-trimethylcyclohexanone and camphor as the organic substrates.

The effect of temperature on the stereochemistry was also evaluated. In these reactions 3,3,5-trimethylcyclohexanone and camphor were reduced by $[(i\text{-}Pr)_2N]_2AlH$ in diethyl ether solvent.

The general preparation of the hydrides used in these studies is given in the following equations. Equation (1) describes the preparation of the precursor, trimethylamine alane. Equation (2) describes the preparation of the bis(dialkylamino) and bis(diarylamino)alanes.

$$LiAlH_4 + Me_3NHCl \xrightarrow{\text{ØH}} H_3AlNMe_3 + LiCl\downarrow + H_2\uparrow \qquad (1)$$

$$AlH_3NMe_3 + 2(HNR_2) \xrightarrow{\text{ØH}} HAl(NR_2)_2 + Me_3N\uparrow + 2\ H_2\uparrow \qquad (2)$$

The yields in these reactions were quantitative and the $HAl(NR_2)_2$ compounds were found to be stable in benzene over several months at room temperature. Reaction in THF and Et_2O were carried out by adding a small aliquot of a concentrated solution of the hydride in benzene to the organic substrate in the ether solvent.

An additional evaluation of these hydrides was made by reducing selected functional groups. The same hydrides were allowed to react with compounds containing different functional groups for two hours and twenty-four hours. These reactions were run for two different periods

of time in order to evaluate the possibility of reducing one functional group in the presence of another. The functional group reductions were carried out in benzene solvent, and several interesting results were obtained.

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